REMARKS

Claims 1-35 are pending. Claims 1-16 and 28-31 were withdrawn from consideration by the Examiner as directed to non-elected inventions. Rejoinder of non-elected method claims is requested upon an indication that an elected product claim is allowable. In satisfaction of their duties of candor and good faith, Applicants bring to the attention of the Examiner the related subject matter in Application Nos. 09/738,879, 09/950,003, 10/240,606, 10/274,706, 10/484,883, 10/496,037, 10/518,229, 10/518,302, 10/518,303, 10/868,359, 10/902,285, 11/030,156 and 11/440,749. She is invited to consider their prosecution histories in this application. The file wrappers of most, if not all, of these applications are accessible electronically so resubmission of those papers here would be redundant. But, if the Examiner would prefer, Applicants would resubmit them in this application.

Claim 32 was objected to as allegedly informal. Its amendment in accordance with the Examiner's suggestion moots this objection. Insertion of the article --an-- before "active" is supported by the original disclosure.

Claim 17 was rejected as allegedly incomplete. Its amendment in accordance with the Examiner's suggestion moots this rejection. Note that the process limitations of claims 1 and 11 were incorporated in claim 17.

Claim 22 was rejected as allegedly indefinite. Cancellation of the limitation "and presenting an unity (a') at the reducing end of the majority of its chains" moots this rejection. This limitation is not required because it is redundant. Claim 22 depends from claim 18, which defines the structure (a').

The amendments are fully supported by the original disclosure and, thus, no new matter is added by their entry. In accordance with these corrections to the claims, withdrawal of the objection and rejections on page 2 of the Action is requested.

35 U.S.C. 102 – Novelty

A claim is anticipated only if each and every limitation as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The identical

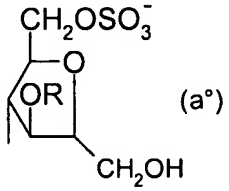
invention must be shown in as complete detail as is claimed. See *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Claims 17-21, 23-25, 27 and 32-35 were rejected under Section 102(b) as allegedly anticipated by Oreste et al. (WO 02/50125). Applicants traverse.

WO 02/50125 discloses a process for the preparation of K5 glycosaminoglycans comprising: (i) N-deacetylation/N-sulfation of the K5 polysaccharide, (ii) partial C5-epimerization of the carboxyl group of the glucuronic acid moiety to the corresponding iduronic acid moiety, (iii) oversulfation, (iv) selective O-desulfation comprising treating the oversulfated product obtained in (iii) with a mixture of methanol/dimethyl sulfoxide for a period of time from 135 to 165 minutes, (v) optional 6-O-sulphation, and (vi) N-sulfation; whatever product obtained at the end of one of (ii) to (vi) being optionally depolymerized.

Referring to the last optional depolymerization, WO 02/50125 discloses a series of processes for preparing depolymerized products, but only the depolymerization with subsequent reduction by sodium borohydride after (vi) is specifically described (see the last paragraph of page 14 and the first and second paragraphs of page 15). The cited document neither specifically discloses a process wherein the depolymerization is carried out at the end of a reaction other than in (vi) nor does it give specific conditions leading to the final products of the claims.

Although WO 02/50125 is silent on the chemical structure at the reducing end of the majority of the chains, anyone of ordinary skill in the art would recognize that the process described in the cited document (i.e., deaminative depolymerization at the end of (vi), followed by reduction with sodium borohydride) provides products that are characterized by the structure (a°)

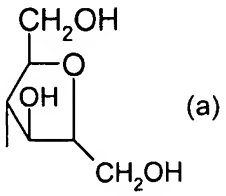


(a°)

wherein R is hydrogen or SO_3^- at the reducing end of the majority of their chains as described, for example, in IT MI2002A001346 (see also PCT/IB03/02338, which was

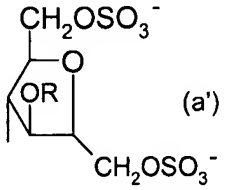
published as WO 03/104505) which was not yet published on the effective filing date of this application, but is cited and incorporated by reference on page 7 of this specification.

Here, in the process recited in Applicants' pending claims, the starting epiK5-N-sulfates are characterized by the structure (a)



(a)

while all the other intermediates as well as the final products are characterized by the structure (a')



(a')

at the reducing end of the majority of their chains.

The process to obtain the products of Applicants' claims 17-27 is a nonobvious variation of the process recited in claim 4 of WO 02/50125. The final products claimed in this application have a different chemical structure and completely different properties as compared to the corresponding low molecular weight products described in WO 02/50125. The latter is discussed below when addressing the Section 103 rejection.

Finally, on the effective filing date of this application, the starting depolymerized (by nitrous depolymerization) epiK5-N-sulfates were new products because they would have been described for the first time in WO 03/106504, which was published on 24 December 2003 (i.e., after the effective filing date of this application). Thus, the starting products used in the process recited in pending claim 17 were not known in the prior art.

To summarize, the products of claims 17-27 are novel over WO 02/50125. Additionally, the claimed products are nonobvious and have properties that were unexpected at the time of the effective filing date of this application. The latter is discussed below when addressing the Section 103 rejection.

The subject matter of claims 32-35 is a pharmaceutical composition comprising an (epi)K5-amine-O-oversulfate-deivative having a sulfation degree of from 2 to 4: i.e., a high- or low-molecular-weight, C5-epimerized or C5-non-epimerized K5 polysaccharide having the amino group of the glucosamine subunit in free form and sulfate groups on oxygen atoms only (see, for example, the products of formula II) in admixture with a pharmaceutical carrier.

Heretofore, only (epi)K5-amine-O-oversulfate-derivatives were used, optionally after an O-desulfation and a 6-O-sulfation, as intermediates for the synthesis of corresponding N-sulfated or N-acylated products. For this purpose, the (epi)K5-amine-O-oversulfate-derivatives were either directly N-sulfated or N-acylated (see WO 03/106504 and WO 03/106505, which were not yet published at the effective filing date of this application), or converted into their pyridine salt and then O-desulfated in dimethylformamide and methanol (see, for example, WO 02/50125).

In accordance with Applicants' invention, the discovery of their high antimicrobial (in particular, antiviral) activity supports our claims to a pharmaceutical composition comprising the (epi)K5-amine-O-oversulfate-derivatives as active ingredients in admixture with a pharmaceutical carrier, in particular as formulations for local administration (see paragraphs [0047]-[0048] and [0134]-[0140] of this specification as published in US 2007/0155694 A1). At the effective filing date of this application, the prior did not teach or suggest any pharmaceutical composition comprising an (epi)K5-amine-O-oversulfate-derivative. Therefore, the compositions of claims 32-35 are novel over WO 02/50125. Additionally, the nonobviousness and unexpected properties of the products contained in the claimed composition are discussed below when addressing the Section 103 rejection.

Withdrawal of the Section 102 rejection is requested because the cited document fails to disclose all limitations of the claimed invention.

35 U.S.C. 103 – Nonobviousness

A claimed invention is unpatentable if the differences between it and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art. *In re Kahn*, 78 USPQ2d 1329, 1334 (Fed. Cir. 2006) citing the legal standard provided in *Graham v. John Deere*, 148 USPQ 459 (1966). The *Graham* analysis needs to be made explicitly. *KSR v. Teleflex*, 82 USPQ2d 1385, 1396 (2007). It requires findings of fact and a rational basis for combining the prior art disclosures to produce the claimed invention. See id. ("Often, it will be necessary for a court to look to interrelated teachings of multiple patents . . . and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue"). The use of hindsight reasoning is impermissible. See id. at 1397 ("A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning"). Thus, a prima facie case of obviousness under Section 103(a) requires "some rationale, articulation, or reasoned basis to explain why the conclusion of obviousness is correct." *Kahn*, 78 USPQ2d at 1335; see *KSR*, 82 USPQ2d at 1396. An inquiry should be made as to "whether the improvement is more than the predictable use of prior art elements according to their established functions." Id. at 1396. But a claim which is directed to a combination of prior art elements "is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." Id. at 1396. Finally, a determination of prima facie obviousness requires a reasonable expectation of success. See *In re Rinehart*, 189 USPQ 143, 148 (C.C.P.A. 1976).

Claims 22 and 26 were rejected under Section 103(a) as allegedly unpatentable over Oreste et al. (WO 02/50125) in view of Naggi et al. (Carbohydrate Res. 336:283-290, 2001). Applicants traverse because the nonobviousness of the claimed products is evident from the evidence of record in this application.

The Naggi document discloses the oversulfation of heparin. The resultant over-sulfated low-molecular-weight (LMW) heparin, which is submitted to a solvolytic, partial O-desulfation and to a N-resulfation of the partially O-desulfated product, is used to obtain a product containing up to 40% O-sulfo groups in both the 6 and 3 positions of the glucosamine subunit and having an anti-Xa activity similar to that of LMW heparin.

In comparison to the process disclosed in WO 02/50125, Naggi's process lacks 6-O-sulfation and thus results in a low amount of 6-O-sulfo groups (not higher than 40%).

Although Naggi hypothesizes a possible N-sulfation and 6-O-sulfation without, however, giving any result, the product of Example 2 in WO 02/50125 itself already represents progress over the product of Naggi's process because the former shows an anti-Xa activity that is 166 (see page 32, line of 9, where the activity of unfractionated heparin is 100) while Naggi's product has an anti-Xa activity similar to or higher of that of LMW heparin which is known to be lower than that of unfractionated heparin.

Moreover, Naggi discloses the oversulfation of heparin (i.e., a product which is already O-sulfated) while the oversulfation is initially performed on a LMW epiK5-N-sulfate (i.e., a product which is not O-sulfated) in the process recited in Applicants' claims. Since the processes for preparing the claimed products (see the first paragraph on page 9 of Applicants' specification) and the product described in WO 02/50125 are similar, one of ordinary skill in the art would have expected at the effective filing date of this application (as the Applicants themselves had expected) a product having the already satisfactory properties of the WO 02/50125 product instead of true LMW heparin-like products having low antithrombin activity as disclosed and claimed herein. Thus, there would not have been a reasonable expectation of success.

It was alleged in the Office Action that Naggi discloses an increase in anti-Xa activity by sulfation and that one of ordinary skill in the art would have been motivated to increase sulfation content at the 3-position in products disclosed in WO 02/50125 to increase the anti-Xa activity. Applicants strongly disagree.

The properties of the claimed products were unexpected. The products of claims 17-27 have a high content in sulfo groups in the 3-position of the glucosamine subunit, but their anti-Xa is much lower than that of the product in WO 02/50125 because both the anti-Xa and the anti-IIa activities of the product of Example 1 are as high as one-half those of LMW heparin (while the product disclosed in WO 02/50125 show an anti-Xa activity more than 50% higher than that of unfractionated heparin). The whole of their properties renders Applicants' claimed products similar to LMW heparin (see para-graph [0046] of this specification as application published in US 2007/0155694A1). This

unexpected result addressed the need for a LMW heparin-like product obtained from a non-animal source.

The advantageous and desirable properties of Applicants' claimed products as compared to the closest prior art (i.e., WO 02/50125) clearly appear from the data given in the annexed declaration from one of the inventors (i.e., Pasqua Oreste), which themselves confirm the teachings of their specification as filed. In Oreste's declaration, the macroscopic differences in structure and properties of the product of Example 2 in WO 02/50125 and of Example 1 in this specification leap out even at a glance.

The structural differences principally reside in the unexpectedly high 3-O-sulfate content on the glucosamine subunit of products obtained through the process disclosed by Applicants in their specification and, surprisingly, in the absence of iduronic acid 3-sulfate and glucuronic acid 2-sulfate groups notwithstanding the high degree of sulfation of the claimed products as compared to the reference product (see Table 2 of the Rule 132 Declaration by Pasqua Oreste).

These differences are even more evident when examining their biological activity on coagulation parameters: in particular, anti-Xa and anti-IIa activities, which are the most important parameters in the evaluation of potential antithrombotic activity, and APTT activity, which is the main parameter in evaluating anticoagulant as a whole.

Oreste's declaration explains that the product of Example 2 in WO 02/50125 is a powerful antithrombin agent while Applicants' claimed products have only weak antithrombin activity (see Table 3 of the Rule 132 Declaration by Pasqua Oreste). Moreover, the same Table 3 shows that the ratio of anti-Xa activity to anti-IIa activity of the product in WO 02/50125 is more than five times lower than that of Applicants' claimed products, which instead resembles commercially-available LMW heparin. Furthermore, Table 3 shows the anti-Xa activity/APTT activity ratio of the product in WO 02/50125 is about half that of the product from Example 1 of Applicants' specification. Thus, use of Applicants' claimed products are predicted to reduce the risk of hemorrhage in patients.

Finally, the product from Example 1 of Applicants' specification has about half of the activity of commercially-available LMW heparin for both anti-Xa and anti-IIa activities (and resulting in a similar anti-Xa activity/anti-IIa activity ratio) (see Table 2 of the Rule

132 Declaration by Pasqua Oreste). Its ability to increase coagulation time is much lower than that of LMW heparin. Thus, these results confirm the teachings in the first paragraph on page 9 of Applicants' specification (see the last sentence: "a glycosaminoglycan derived from the polysaccharide K5 that may be assimilated to the sLMWH as far as the antiXa/anti-IIa ratio is concerned and that, at equal dosages, presents a 2.5- to 4-fold lower hemorrhagic risk than sLMWH"). In summary, Oreste's declaration confirms that the representative product of Applicants' Example 1 can be assimilated to the standard low molecular weight heparin (sLMWH), with a lower bleeding risk. To Applicants' knowledge, their invention was the first to finally succeed in preparing a semisynthetic, LMW heparin-like product without using animal organs as the raw material.

Based on the combination of the WO 02/50125 and Naggi documents, it would not have been obvious to one of ordinary skill in the art to apply a process similar to that disclosed in WO 02/50125 to a depolymerized (e.g., nitrous depolymerization) low molecular weight epiK5-N-sulfate because it would not have been expected to result in a product having structural and biological properties completely opposite those of the product obtained in accordance with the process of WO 02/50125.

Withdrawal of the Section 103 rejection is requested because the claimed invention would not have been obvious to the ordinarily skilled artisan at the time Applicants made their invention.

Double Patenting

Claims 17-27 and 32-35 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being allegedly unpatentable over claims 37-59 of copending Application No. 11/440,749. Applicants traverse because a terminal disclaimer may be submitted or conflicting claims may be canceled upon an indication of allowable subject matter. To require submission of a terminal disclaimer prior to an indication that the claims are otherwise allowable would constitute an undue burden on Applicants because no allowable subject matter in either application has been indicated by the Patent Office.

Claims 17-27 and 32-35 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being allegedly unpatentable over claims 1-3 and 14-36 of copending Application No. 11/030,156. Applicants traverse because a terminal disclaimer may be submitted or conflicting claims may be canceled upon an indication of allowable subject matter. To require submission of a terminal disclaimer prior to an indication that the claims are otherwise allowable would constitute an undue burden on Applicants because no allowable subject matter in either application has been indicated by the Patent Office.

Claims 17-27 and 32-35 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being allegedly unpatentable over claims 11-25 of copending Application No. 10/868,359. Applicants traverse because a terminal disclaimer may be submitted or conflicting claims may be canceled upon an indication of allowable subject matter. To require submission of a terminal disclaimer prior to an indication that the claims are otherwise allowable would constitute an undue burden on Applicants because no allowable subject matter in either application has been indicated by the Patent Office.

Claims 17-27 and 32-35 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being allegedly unpatentable over claims 1-3 and 35-62 of copending Application No. 09/950,003. Applicants traverse because a terminal disclaimer may be submitted or conflicting claims may be canceled upon an indication of allowable subject matter. To require submission of a terminal disclaimer prior to an indication that the claims are otherwise allowable would constitute an undue burden on Applicants because no allowable subject matter in either application has been indicated by the Patent Office.

Applicants note that a Notice of Abandonment was mailed in Application No. 10/868,359. In the still pending applications, no claims have been indicated as allowed. Therefore, it is premature to address the double patenting rejection at this time.

Conclusion

Having fully responded to the Office Action, Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if any further information is required.

Respectfully submitted,

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